REMARKS

This application is owned by Seahorse Bioscience, Inc., a private start-up located in Billerica, Mass, which has developed a beta version bench-top, non-invasive cellular assay device sold under the trademark "XF24". The Examiner is invited to inspect the Seahorse web site at http://www.seahorsebioscience.com/ for information concerning the subject matter of this application. Seahorse now has sold multiple machines which in operation practice various of the methods claimed herein to pharmaceutical companies and academic institutions, and feedback has been very positive.

At the outset Applicants thank the Examiner for his resourceful examination of the presented claims. Applicants believe that the Examiner will agree that nothing in the cited art discloses or renders obvious the subject matter *disclosed in the specification*, and that prosecution properly should focus on the form and breadth of the claims covering various aspects of Applicants' inventions so as to more clearly define their invention and to clearly patentably distinguish it from the cited art. To that end, all claims as now presented are submitted to be limited to clearly novel and non obvious subject matter, and to be in condition for allowance, for the reasons outlined below.

Status of Claims

Claims 1, 2, 19, 20, and 31 have been amended. Claims 14-16 and 40-80 are hereby cancelled without prejudice. New dependent claims 81- 95, including new independent claim 84, have been added. After entry of this amendment, this application will contain claims 1-13, 17-39, and 41 -95. Independent claim 1 has been amended to more particularly define the invention over the applied art, and to obviate the 102, 103, and 112 rejections. All claims as presented are limited to the subject matter restricted by the Examiner and elected by Applicants. No new matter has been introduced. The newly added claims are presented to cover certain preferred methods of the invention more particularly.

Rejection Under 35 U.S.C. § 112

The objection to the specification has been obviated by amendment.

The preambles of independent claim 1 and new independent claim 84 now require analyzing cells disposed in media within a vessel *by analyzing constituents extracted from or secreted into* the media. Accordingly, the 112 rejection, to the extent applied to the claims as amended, and any confusion, has been obviated.

Rejection Under 35 U.S.C. § 102

As the Examiner no doubt is aware, a proper 102 rejection requires that every limitation set forth in the claims be disclosed explicitly or inherently in a single prior art reference. Applicants submit that the rejection based on the applied Seaver et al reference falls far short of this standard and is improper. Nevertheless, Applicants have amended the claims to very clearly distinguish them from the disclosure of Seaver, and to more particularly claim so that the broad interpretation accorded by the Examiner to claims 1-7, 10, 17-20, 22, 26, 27, 34, 35, and 36 are now clearly untenable. Specifically, claims 1-39 and 81-83, in their current form, all require (among other distinguishing limitations), in the order stated (note step c. necessarily comes after step b., and step d. after step c.):

> (1) reducing the original volume *in the vessel* to define a reduced volume of media; then (2) analyzing a constituent related to the cells *within the reduced volume* of media *in the vessel*; and (3) *increasing the reduced volume of media about the cells in the vessel.*

Thus, as amended, claim 1 requires that *in the same vessel* the media volume is reduced, the media constituent is analyzed, and the media volume is restored (thus permitting the cells to continue in a living state).

Nothing in the Seaver reference suggests this, and accordingly this rejection is improper to the extent applied to the claims as amended. Note Seaver, among other deficiencies, discloses analysis of extracellular component in aliquots sampled from the mother culture at various times,

and fails to disclose analysis of any constituent within a reduced volume of media within the vessel.

Rejection Under 35 U.S.C. § 103

Reconsideration and withdrawal of the various 103 rejections is requested in view of the amendments to the claims and the argument which follows.

None of the references, alone or in combination, can fairly be said to make obvious to a person of skill in the art the subject matter as now claimed, taken as a whole, nor remotely to suggest that which Applicants have now claimed. The Examiner apparently has read Applicants' claims and specification, then sought disparate references disclosing individually some of the various limitations set forth in the dependent claims, and then pieced these disclosures together to reject the claims for "obviousness." Were this the standard of obviousness, no claim could be issued, as all claims necessarily are combinations of elements known in the art.

In this case, the method aspect of Applicants' invention are now carefully and distinctly articulated. None of the references, individually or together, disclose analyzing *extracellular* constituents by reducing the volume of the cell media, conducting the analysis of the extracellular constituent on the media in the reduced volume (thereby increasing sensitivity), and then increasing the volume of the media, as specifically required in each of claims 1-39, and 81 - 83. Furthermore, none of the references disclose a process involving reduction of media volume followed by analysis of extracellular constituents in the reduced volume, nor such a process involving use of a sensor in contact with a reduced media volume. Thus the subject matter of claims 84-89 clearly are free of all applied art.

Not only do the applied references fail to suggest that which Applicants have claimed, but nothing in the various references suggests that they should be combined *for any purpose*, or that there could or would be any advantage in combining them. Furthermore, even if combined they do not result in the method claimed, and do not and cannot achieve the combination of advantages which inure to Applicants' invention.

The deficiencies of Seaver et al. are discussed above. Of the applied references, only Terasaki is believed to disclose reducing cell media volume. However, Applicants have been unable to find any suggestion in Terasaki of conducting an assay *of extracellular constituents* therein. Rather, a technician views the cells directly to observe lymphocyte cytotoxicity, and the "solid rod displaces test solution from the optical view path thereby reducing the depth of solution which must be viewed through" (Col 3 lines 7-10). Ferguson discloses how to make and use fiber optic sensors allowing several gases to be analyzed simultaneously in cultures of beer making organisms. Applicants can find no hint in Ferguson that such sensors can or should be used in a method such as is claimed herein. Applicants have been unable to find in Ferguson a disclosure or suggestion of, nor recognition of any importance to, a change in volume of cell medium. The Criddle reference discloses isothermal measurement of metabolic heats *in an ampule*, that is, a sealed small glass or plastic bulb. Applicants submit Criddle contains no disclosure relevant to Applicants' claims as amended.

CONCLUSION

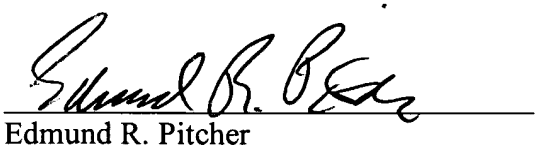
In light of the foregoing, Applicants respectfully submit that all claims are now in condition for allowance.

If the Examiner believes that a telephone conversation with Applicants' attorney would expedite allowance of this application, the Examiner is cordially invited to call the undersigned attorney at (617) 570-1780.

A petition for a three-month extension of time to respond to the Office action is attached, and a supplemental Information Disclosure Statement, as well as a check for $1200 for the requisite fees.

Applicants believe that no additional fee is due for filing of this amendment. However, if any fee is due, please charge any such fee occasioned by this paper to our Deposit Account No. 07-1700.

Respectfully submitted,



Date: December 15, 2006
Reg. No. 27,829

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